(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 May 2001 (03.05.2001)

PCT

(10) International Publication Number
WO 01/30760 A1

(51) International Patent Classification[7]: C07D 231/44, 401/04

(21) International Application Number: PCT/EP99/08687

(22) International Filing Date: 22 October 1999 (22.10.1999)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

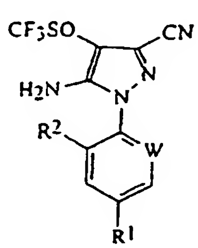
Published:

— *With international search report.*

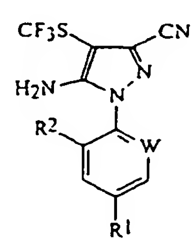
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING 4-TRIFLUOROMETHYLSULPHINYLPYRAZOLE DERIVATIVE



(I)



(II)

(57) Abstract: A process for the preparation of a compound of formula (I), R^1 represents halogen, haloalkyl, haloalkoxy, $R^4S(O)_n$-, or -SF_5; R^2 represents hydrogen or halogen; R^3 represents halogen; R^4 represents alkyl or haloalkyl; and n represents 0, 1 or 2; which process comprises oxidising a compound of formula (II); wherein R^1, R^2 and W are as defined above, with trifluoroperacetic acid in the presence of a corrosion inhibiting.

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PROCESS FOR PREPARING 4-TRIFLUOROMETHYLSULPHINYLPYRAZOLE DERIVATIVE

This invention relates to improved processes for preparing 1-arylpyrazole pesticides such as 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole known as Fipronil (Pesticide Manual 11th Edition), and for the intermediates used in its preparation 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole and 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide.

European Patent Publication No.295117 describes the preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole by the oxidation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole with 3-chloroperbenzoic acid. The use of trifluoroacetic acid and hydrogen peroxide (forming trifluoroperacetic acid <u>in situ</u>) for the oxidation of sulphides to sulphoxides and/or sulphones is known and is generally useful for the oxidation of electron deficient sulphides such as trifluoromethylsulphides which are less readily oxidised than other sulphides. Such procedures have been reported in the literature, for example in the preparation of certain 1-arylpyrazole pesticides.

A problem encountered in the preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole by the oxidation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole is the co-formation of the corresponding sulphone compound 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphonylpyrazole, which is difficult to remove from the sulphoxide. A number of oxidants (including amongst others sodium vanadate, sodium tungstate, peracetic acid, performic acid and pertrichloroacetic acid) have been employed in an attempt to obtain

an efficient and regioselective oxidation which will provide 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole in pure form and which may also be utilised for large scale preparations. All of the above methods were found to be unsatisfactory in one respect or another.

It has now been found that a mixture of trifluoroacetic acid and hydrogen peroxide (trifluoroperacetic acid) gives excellent results in terms of both selectivity and yield.

However a problem of using the trifluoroacetic acid and hydrogen peroxide mixture on large scales is that it leads to corrosion of the glass linings of industrial reaction vessels, which is rapid (typically 300μm/year) even at ambient temperatures, whilst at $80^{O}C$ the speed of corrosion increases to about 1430μm/year. This corrosion occurs as a result of the formation of hydrogen fluoride, and therefore prohibits the use of this reagent mixture in such vessels.

It has now been found that the addition of a corrosion inhibiting compound such as boric acid to the reaction mixture inhibits the corrosion process and reduces the speed of corrosion to a level that is typically less than 5μm/year.

European Patent Publication No. 0374061 and J-L.Clavel et.al. in J.Chem.Soc.Perkin I, (1992), 3371-3375 describe the preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide, and the further conversion of this disulphide to the pesticidally active 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole by reaction with trifluoromethyl bromide in the presence of sodium formate and sulphur dioxide in N,N-dimethylformamide in an autoclave at low pressure (typically 13 bars) at $60^{O}C$.

However on larger scales the reaction is very exothermic which results in a substantial pressure increase in the vessel and associated operator hazard.

Moreover it is necessary to add the trifluoromethyl bromide quickly (generally within 0.5 hour), because the mixture of disulphide, sodium formate, sulphur dioxide and N,N-dimethylformamide has been found to be unstable (typically leading to 55% degradation into unwanted by-products within 2 hours at $50^{o}C$). This requirement for rapid addition of trifluoromethyl bromide is not compatible with the exothermic nature of the reaction.

In order to overcome these problems and develop a process which can be used on a large scale other conditions have been sought.

In the above described procedures the reaction was performed by addition of the trifluoromethyl bromide to a mixture of the other components. A new process has now been developed in which the order of addition is different.

European Patent Publication No. 0374061 describes the preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide by the reaction of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-thiocyanatopyrazole with base, and the further conversion of this disulphide to the pesticidally active 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole.

European Patent Publication No. 295117 discloses a process for the preparation of 1-aryl-3,5-disubstituted-pyrazol-4-yl disulphides by the hydrolysis of the corresponding 4-thiocyanatopyrazole derivatives using hydrochloric acid in ethanol, or by reduction using sodium borohydride in ethanol, or by treatment with aqueous sodium hydroxide under phase transfer conditions in the presence of chloroform and benzyltriethylammonium chloride.

The preparation of the above 5-amino-1-aryl-3-cyano-4-thiocyanatopyrazole intermediates is also described in European Patent Publication Numbers 0374061 and 295117, and these are obtained by the thiocyanation of the corresponding 5-amino-1-aryl-3-cyanopyrazole derivatives using an alkali metal or ammonium thiocyanate in the presence of bromine and methanol at low temperature.

The above 2-step process for the preparation of 5-amino-1-aryl-3-cyanopyrazol-4-yl disulphide intermediates from 5-amino-1-aryl-3-cyanopyrazoles presents several problems which limit its usefulness for application on large scales:

i) the thiocyanation step is generally performed at very low temperatures,

ii) the mixture of bromine and methanol used in the thiocyanation reaction may form explosive mixtures,

iii) the above reactions involve heterogeneous mixtures, and

iv) it is difficult to obtain complete transformations to product in either reaction stage.

In order to overcome these problems other conditions have been sought. Thus the explosive hazard may be avoided in the thiocyanation reaction by replacing the methanol with a mixture of dichloromethane and water, however this procedure is not efficient on large scales.

The thiocyanation reaction may alternatively be successfully carried out using an alkali metal or ammonium thiocyanate in the presence of hydrogen peroxide and a mineral acid such as hydrochloric acid in a solvent such as an alcohol for example methanol. An improved procedure for the subsequent hydrolysis step has been found which involves the use of a base such as an alkali metal hydroxide, for example sodium hydroxide, in the presence of formaldehyde and a solvent such as aqueous methanol, however the disulphide thus obtained is very powdery and difficult to filter. Furthermore in order to obtain the above disulphide in satisfactory quality it is necessary to subject the starting

material 5-amino-1-aryl-3-cyanopyrazole to additional purification before it is used in the thiocyanation and hydrolysis reactions.

Hence it may be appreciated that the above 2-step procedure is inefficient for an industrial process, and a single step method lacking these disadvantages would clearly be preferred.

The present invention seeks to provide improved or more economical methods for the preparation of pesticides.

It is a first object of the present invention to provide a convenient process for preparing 5-amino-1-aryl-3-cyano-4-trifluoromethylsulphinylpyrazole pesticides, which are obtained in high yield and high purity.

It is a further object of the present invention to provide a process for preparing 5-amino-1-aryl-3-cyano-4-trifluoromethylsulphinylpyrazole pesticides which is simple and safe to perform, and which results in minimal vessel corrosion.

It is a further object of the present invention is to provide a process for the preparation of 5-amino-1-aryl-3-cyano-4-trifluoromethylsulphinylpyrazole pesticides which includes an efficient recovery procedure for the trifluoroacetic acid.

It is a further object of the present invention to provide a convenient process for preparing 5-amino-1-aryl-3-cyano-4-trifluoromethylthiopyrazole pesticides and pesticidal intermediates, which are obtained in high yield and high purity with improved transformation of the 5-amino-1-aryl-3-cyanopyrazol-4-yl disulphide.

It is a further object of the present invention to provide a process for preparing 5-amino-1-aryl-3-cyano-4-trifluoromethylthiopyrazole pesticides and pesticidal intermediates, which is simple and safe to perform, is operated at lower pressures and temperatures, and in which side reactions are minimised.

It is a further object of the present invention to provide a convenient process for preparing 5-amino-1-aryl-3-cyanopyrazol-4-yl disulphide pesticidal intermediates, which are obtained in high yield and high purity.

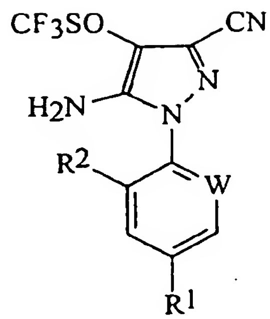
It is a further object of the present invention to provide a single step process for preparing 5-amino-1-aryl-3-cyanopyrazol-4-yl disulphide pesticidal intermediates from 5-amino-1-aryl-3-cyanopyrazole intermediates.

It is a further object of the present invention to provide a process for preparing 5-amino-1-aryl-3-cyanopyrazol-4-yl disulphide pesticidal intermediates which is simple and safe to perform, utilises readily available materials, allows efficient isolation of the product and does not require additional purification of the 5-amino-1-aryl-3-cyanopyrazole starting material.

It is a further object of the present invention to provide a convenient process for preparing 5-amino-1-aryl-3-cyano-4-trifluoromethylsulphinylpyrazole pesticides by a three step process starting from 5-amino-1-aryl-3-cyanopyrazoles.

These and other objects of the invention will become apparent from the following description, and are achieved in whole or in part by the present invention.

According to a feature of the present invention there is provided an improved process (A) for the preparation of a compound of formula (I):



(I)

wherein W represents nitrogen or $-CR^3$;

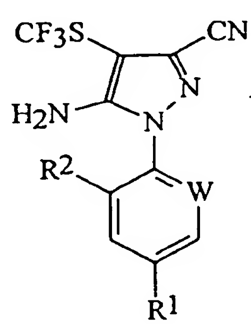
R^1 represents halogen, haloalkyl (preferably trifluoromethyl), haloalkoxy (preferably trifluoromethoxy), $R^4S(O)_n$-, or $-SF_5$;

R^2 represents hydrogen or halogen (for example chlorine or bromine);

R^3 represents halogen (for example chlorine or bromine);

R^4 represents alkyl or haloalkyl; and

n represents 0,1 or 2; which process comprises oxidising a compound of formula (II):



(II)

wherein R^1, R^2 and W are as hereinbefore defined, with trifluoroperacetic acid in the presence of a corrosion inhibiting compound.

In a preferred embodiment of the invention the trifluoroperacetic acid is generated <u>in situ</u> by the reaction of trifluoroacetic acid and hydrogen peroxide. Accordingly, this embodiment comprises treating a

compound of formula (II) as defined above with trifluoroacetic acid and hydrogen peroxide.

Unless otherwise specified in the present specification 'alkyl' means straight- or branched- chain alkyl having from one to six carbon atoms (preferably one to three). Unless otherwise specified 'haloalkyl' and 'haloalkoxy' are straight- or branched- chain alkyl or alkoxy respectively having from one to six carbon atoms (preferably one to three) substituted by one or more halogen atoms selected from fluorine, chlorine and bromine.

When R^1 represents $R^4S(O)_n$- and n is 0 or 1, the process may bring about oxidation to the corresponding compound in which n is 1 or 2, respectively.

The corrosion inhibiting compound is generally boric acid or an alkali metal borate such as sodium borate; or any hydrogen fluoride trapping agent such as silica (silicon dioxide), optionally in the form of silica oil. Preferably the corrosion inhibiting compound is boric acid.

The amount of corrosion inhibiting compound used is generally 0.08-0.22 molar equivalents, and preferably about 0.08-0.1 molar equivalents.

The amount of trifluoroacetic acid employed is generally from 14-15 molar equivalents.

The amount of hydrogen peroxide influences the reaction since an excess will lead to the formation of the corresponding sulphone of the compound of formula (I), whilst a deficiency will lead to incomplete transformation, and in either event an impure final product is obtained. Thus the amount of hydrogen peroxide used in the reaction (generally as a 35% aqueous solution) is generally from 1.3-1.5 equivalents, preferably about 1.31-1.35 equivalents and more preferably about 1.33 equivalents.

The reaction is generally performed at a temperature of from 10-15°C and preferably at about 12°C.

A further problem associated with the use of trifluoroacetic acid and hydrogen peroxide concerns the recovery and recycling of the expensive trifluoroacetic acid which is essential for the operation of an economically efficient process. In one procedure that was developed in an attempt to solve this problem, the reaction mixture was quenched with sulphur dioxide and a part of the trifluoroacetic acid removed by distillation. An excess of ethanol was then added to the residue to form ethyl trifluoroacetate which was then removed by distillation. The product was then crystallised from a mixture of ethanol/water. This procedure was found to have two disadvantages:

i) the ethanol/water mixture does not provide sufficiently pure 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole; and

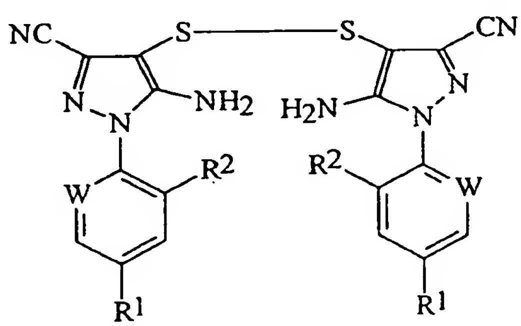
ii) the recycling of trifluoroacetic acid via the acid hydrolysis of ethyl trifluoroacetate is a complex process on a large scale and generates a large quantity of unwanted sodium sulphate thus presenting a waste problem.

A new procedure has now been found which solves both of these problems and thus provides a simple and efficient method for the preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole in high yield and purity, and in addition provides an efficient recovery procedure for trifluoroacetic acid. In this process, when the reaction in trifluoroacetic acid and hydrogen peroxide is judged to be complete, the excess of hydrogen peroxide is generally quenched with sulphur dioxide (or equivalent reagent), chlorobenzene is added and the trifluoroacetic acid removed by distillation. Typically the trifluoroacetic acid is removed by azeotropic distillation under reduced pressure. An alcohol such as methanol, ethanol or isopropanol (preferably ethanol) is then added to the residue

and warmed to about 80^{o}C until a solution is formed, and then cooled to about 40^{o}C when the 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole crystallises. The alcohol is evaporated at 40^{o}C under reduced pressure, the mixture cooled to about 0^{o}C, filtered, and the product washed and dried in vacuo. Chlorobenzene has been found to be the only industrial solvent which is compatible with the mixture, has a boiling point significantly higher than that of trifluoroacetic acid, and allows crystallisation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole in good yield and quality.

Thus a preferred aspect of the process of the invention as described above further comprises adding chlorobenzene to the reaction mixture on completion of the oxidation reaction, and recovering the trifluoroacetic acid by distillation.

According to a further feature of the present invention there is provided an improved process (B) for the preparation of a compound of formula (II) as defined above; which process comprises the addition of sulphur dioxide to a mixture comprising a disulphide of formula (III):



(III)

wherein R^1, R^2 and W are as hereinbefore defined, a formate salt, trifluoromethyl bromide and a polar solvent. The polar solvent is generally selected from N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulphoxide,

sulpholane, hexamethylphosphoramide and ethers such as dioxan, tetrahydrofuran and dimethoxyethane. It is preferably N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulphoxide or sulpholane, more preferably N,N-dimethylformamide.

The advantages of performing the process with this order of addition are:

i) the mixture of disulphide of formula (III), sodium formate, trifluoromethyl bromide and polar solvent (preferably N,N-dimethylformamide) is stable and so the sulphur dioxide may be added more slowly without risk of degradation, thus providing a more convenient and safe process,

ii) the new process is efficient being characterised by good yields of product and high transformation of disulphide, and

iii) the rate of addition of sulphur dioxide may be controlled so that any increase in the reaction temperature and/or pressure can be maintained at a safe level, thus allowing large scale reactions to be performed safely (including for example typical commercial reactors having about $15 m^3$ volume).

The formate salt is generally an alkali metal or ammonium salt, preferably sodium formate.

The reaction temperature during the addition of the sulphur dioxide is generally from 35-55^{o}C, preferably from about 35-50^{o}C, most preferably from about 43-47^{o}C, which allows efficient control of the heat from the exothermic reaction. Below 35^{o}C the reaction tends to proceed too slowly to be useful for an industrial process. At temperatures above 55^{o}C the yield and quality of product is reduced.

The sulphur dioxide is generally added at such a rate that the temperature is maintained within the above defined range. On large

scales this is generally carried out over a 0.5-2 hour period, preferably during about 1-1.5 hours. An addition time of about 1-1.5 hours has been shown to be optimal in minimising the formation of by-products.

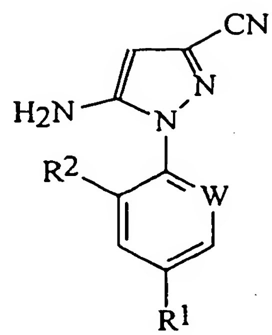
The molar ratio of trifluoromethyl bromide:disulphide of formula (III) is preferably from 3:1 to 5:1. It is convenient to employ a molar ratio of about 3:1.

The amount of sulphur dioxide used is generally from 1.2-1.5 molar equivalents relative to the disulphide of formula (III) and preferably about 1.3 molar equivalents. When only 1 equivalent is employed the yield of product is lowered and transformation of disulphide tends to be incomplete, whilst an excess of sulphur dioxide leads to degradation during evaporation of the solvent in the work-up.

The amount of formate salt used is generally 4-6 molar equivalents relative to the disulphide of formula (III), preferably about 4.5-5.5 molar equivalents. A joint reduction in the amount of sulphur dioxide and formate salt can be made until the ratio of sulphur dioxide:disulphide is from about 1.2:1 and the ratio of formate salt:disulphide is from about 4.5:1.

By using the process according to the above description the pressure in the vessel is generally easily maintained in the safe range of 3-6 bars.

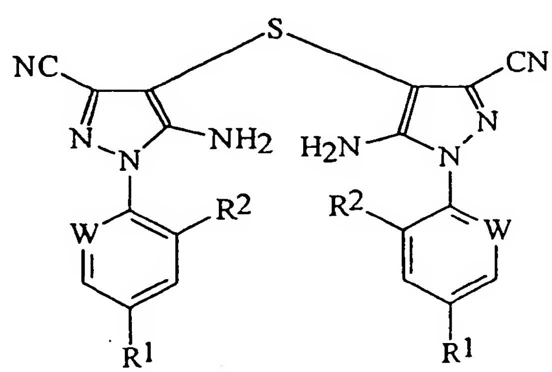
According to a further feature of the present invention there is provided a process (C) for the preparation of a disulphide of formula (III) as defined above; which comprises adding sulphur monochloride (S_2Cl_2) to a solution in an organic solvent of a compound of formula (IV):



(IV)

wherein R^1, R^2 and W are as hereinbefore defined.

The reaction is preferably conducted in a solvent selected from toluene, dichloromethane or dichloroethane, or aliphatic or aromatic nitriles such as acetonitrile, propionitrile, methylglutaronitrile and benzonitrile; or mixtures thereof, optionally as a mixture with chlorobenzene (which is present when a chlorobenzene solution of the compound of formula (IV) obtained from the previous reaction stage is used). Acetonitrile optionally in the presence of chlorobenzene is the preferred solvent for the reaction. The reaction is very sensitive to the effect of solvent and whilst it may be convenient to use toluene since a toluene solution of (IV) may be available from the previous reaction stage, a significant amount of the monosulphide (V):



(V)

is generally formed as a by product when these conditions are employed. Moreover the product is very slow to filter when toluene is employed, although an acceptable filtration rate may be obtained by addition of a proportion of acetonitrile to the toluene solution. When the reaction is performed in the preferred solvent acetonitrile, the amount of monosulphide impurity (V) is reduced and the rate of filtration of the product (III) is satisfactory.

The sulphur monochloride used in the process is generally from 99.4-99.9% w/w pure.

The quality of solvent used may affect the reaction since the presence of certain impurities can influence the yield of product (with the formation of (V) as by-product). Thus when acetonitrile is employed as solvent it is preferred that the content of water is <1000ppm, the content of ethanol is <1500ppm and the content of ammonia is <100ppm. It is also preferable to avoid the presence of even low amounts of acetone or N,N-dimethylformamide in the solvent mixture since, for example, the presence of about 100ppm of acetone in dichloromethane may have a negative impact on the yield of product.

The order of addition of the reagents is an important feature of the reaction. Thus it is very important to add the sulphur monochloride to a solution of compound of formula (IV) (rather than the reverse). A rapid addition time for the sulphur monochloride is a preferred feature of the process. Thus if the sulphur monochloride is added during 1 minute, the disulphide (III) crystallises about 15 seconds after the completion of the addition (and all of the compound of formula (IV) has been consumed). When added over a 15 minute period the disulphide (III) crystallises in mid-addition and as a result the disulphide (III) co-crystallises with the remaining compound of formula (IV). Washing the impure product so obtained with a large excess of acetonitrile does not effect removal of the unreacted compound of formula (IV). The time for the sulphur

monochloride addition is preferably from 1-10 minutes, more preferably about 1-5 minutes.

The reaction temperature of the mixture at the start of the addition of the sulphur monochloride is preferably from 5 to 25^{o}C, more preferably from about 10 to 20^{o}C . If the temperature is at 30^{o}C at the start of the addition, a lower yield is obtained due to the formation of trisulphide and tetrasulphide by-products. As the reaction is exothermic the temperature increases during the reaction and is preferably held at from about 20 to 35^{o}C.

The molar ratio of compound of formula (IV): sulphur monochloride used in the reaction is generally from 2:1 to 2:1.06, and preferably from about 2:1 to about 2:1.04. Using a larger excess of sulphur monochloride results in the formation of an increased amount of the monosulphide by-product (V). If a lower proportion of sulphur monochloride is used the reaction does not proceed to completion.

A further feature of the process of the invention is the method used for the purification of the product. Thus the reaction mixture containing the disulphide of formula (III) is first degassed to remove hydrogen chloride, generally by heating at about 40^{o}C under reduced pressure, generally at about 0.2 atmosphere. It is then heated at about 80^{o}C for about 1 hour at atmospheric pressure. After cooling to about 30^{o}C, a weak base (generally ammonia) is added to neutralise any remaining hydrogen chloride and obtain a pH about 6.5-7. The mixture is then cooled to about 5^{o}C and the product isolated by filtration. This procedure enables the disulphide of formula (I) to be obtained in high yield and purity by a simple procedure convenient for large scale operations.

In formulae (I), (II), (III) and (IV), preferred values of the symbols are as follows:-

R^1 represents haloalkyl (preferably trifluoromethyl), haloalkoxy (preferably trifluoromethoxy) or $-SF_5$;

W represents $-CR^3$;

R^2 and R^3 represent halogen (preferably chlorine).

A particularly preferred compound of formula (I) is:

5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole.

A particularly preferred compound of formula (II) is:

5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole.

A particularly preferred compound of formula (III) is:

5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide.

Compounds of formula (II), (III) and (IV) are known.

According to a further feature of the present invention the processes (A), (B) and (C) can be combined to prepare a compound of formula (I) from a compound of formula (IV).

The above processes (A), (B) and (C) when combined together form a particularly useful and efficient method for the preparation of Fipronil.

The following non-limiting examples illustrate the invention.

Example 1

Preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole

Trifluoroacetic acid (1660g, 14.5mol) was added to a stirred solution of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole (436g, 1.03mol) and boric acid (5g, 0.08mol) in a glass reactor at 12°C. Hydrogen peroxide (131.5g of 35%w/w, 1.35mol) was added over 2 hours whilst maintaining the temperature at 12°C, and the mixture kept at this temperature for a

further 4-5 hours. When the transformation had reached 97-98%, or the amount of unwanted 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphonylpyrazole reached 2% (as judged by HPLC analysis), sulphur dioxide was added to quench any remaining hydrogen peroxide, and the mixture maintained at 10-18°C for 0.5 hour. Chlorobenzene (370g) was added and the mixture placed under reduced pressure (from 0.17 to 0.04 atmosphere) and heated to 47-50°C with azeotropic distillation. A homogeneous fraction containing recovered trifluoroacetic acid was obtained. During the distillation additional chlorobenzene (1625g) was added continuously in order to maintain a constant volume. At the end of the azeotropic distillation the reactor contents were maintained at 47-50°C under reduced pressure (0.04 atmosphere), and a homogeneous fraction of chlorobenzene distilled. After release of the vacuum, the reactor was heated to 40°C, ethanol (207g) and chlorobenzene (235g) added, and the mixture heated to 80°C with stirring to give a solution. On cooling to 40°C the product crystallised. The reactor was placed under progressively reduced pressure (from 0.13 to 0.03 atmosphere) and the ethanol distilled at 40°C. The vacuum was released and the mixture cooled to 5°C during 3.5 hours and left for a further 0.5 hour. The product was filtered off, washed with cold chlorobenzene, then with cold aqueous ethanol, then with water, and dried in vacuo at 135°C to give the title compound (407.5g), in a typical yield of 89% and purity of 95.5%.

Example 2

Preparation of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylthiopyrazole

Sodium formate (76g, 1.11mol) was added to a mixture of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide (157.5g, 0.223mol) and N,N-dimethylformamide (643g) in a glass reactor. After purging with nitrogen at 2 bars, the reactor was sealed and trifluoromethyl bromide (101g, 0.682mol) added. The reactor

was heated to 45°C and sulphur dioxide (19.5g, 0.304mol) added over 1.5 hours and the temperature maintained between 43°C and 47°C during the reaction and for a further 0.75 hour. The pressure was released to effect degassing for 1.5 hours, with cooling of the vessel to 25-30°C 1 hour after the release of pressure. When the internal pressure reached atmospheric pressure the mixture was treated with sodium bicarbonate and the N,N-dimethylformamide partially evaporated whilst heating to 50-70°C at reduced pressure. The residue was cooled to 40°C and added slowly to water with stirring at 20-25°C. The product was filtered, washed (hot water) and dried in vacuo at 100°C to give the title compound (182.3g) in typical yields of 95% and purity of 96.6%.

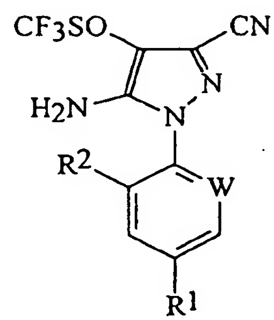
Example 3

Preparation of 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide

Acetonitrile (837g) was added to a chlorobenzene solution (627.8g) which contained 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazole (366.6g, 1.14mol). The mixture was heated at 50-64°C under reduced pressure (0.5 atmosphere) and dried by the distillation of about 45ml of the acetonitrile. After cooling to 18°C, sulphur monochloride (77g, 0.57mol) was added rapidly over 1 minute. The temperature of the mixture increased to 35°C and was maintained at 35°C by cooling until the exotherm ceased and for a further 0.3 hour. The mixture was then degassed (to remove hydrogen chloride) by heating at 40°C under reduced pressure, and then heated at 80°C for 1 hour at atmospheric pressure. After cooling to 30°C, ammonia was added to bring the pH to 6.5-7, cooled to 5°C and the product filtered off, washed with chlorobenzene/acetonitrile and dried at 95°C under vacuum to give the title compound (365.2g) in typical yield of 89.4% and 98.4% purity.

CLAIMS

1. A process (A) for the preparation of a compound of formula (I):



(I)

wherein W represents nitrogen or $-CR^3$;

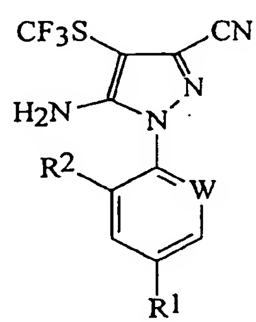
R^1 represents halogen, haloalkyl, haloalkoxy, $R^4S(O)_n$-, or $-SF_5$;

R^2 represents hydrogen or halogen;

R^3 represents halogen;

R^4 represents alkyl or haloalkyl; and

n represents 0,1 or 2; which process comprises oxidising a compound of formula (II):



(II)

wherein R^1, R^2 and W are as defined above, with trifluoroperacetic acid in the presence of a corrosion inhibiting compound.

2. A process according to claim 1 in which the trifluoroperacetic acid is generated in situ by the reaction of trifluoroacetic acid and hydrogen peroxide.

3. A process according to claim 1 or 2 in which the corrosion inhibiting compound is boric acid.

4. A process according to claim 1, 2 or 3 in which the amount of corrosion inhibiting compound used is about 0.08-0.2 molar equivalents.

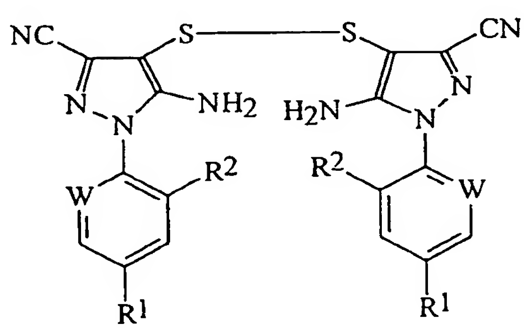
5. A process according to any one of the preceding claims in which the amount of trifluoroacetic acid employed is from 14-15 molar equivalents.

6. A process according to any one of the preceding claims in which the amount of hydrogen peroxide used in the reaction is from 1.3-1.5 equivalents.

7. A process according to any one of the preceding claims in which the reaction is performed at a temperature of from 10-15°C.

8. A process according to any one of the preceding claims which further comprises adding chlorobenzene to the reaction mixture on completion of the oxidation reaction, and recovering the trifluoroacetic acid by distillation.

9. A process (B) for the preparation of a compound of formula (II) as defined in claim 1; which process comprises adding sulphur dioxide to a mixture comprising a disulphide of formula (III):



(III)

wherein R^1, R^2 and W arc as defined in claim 1, a formate salt, trifluoromethyl bromide and a polar solvent.

10. A process according to claim 9 in which the solvent is N,N-dimethylformamide.

11. A process according to claim 9 or 10 in which the reaction temperature during the addition of the sulphur dioxide is from 35-55^{o}C .

12. A process according to claim 9, 10 or 11 in which the sulphur dioxide is added ovcr a 0.5-2 hour period.

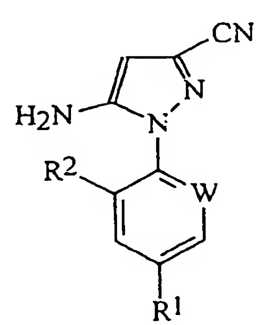
13. A process according to any one of claims 9 to12 in which the molar ratio of trifluoromethyl bromide:disulphide of formula (III) is from 3:1 to 5:1.

14. A process according to any one of claims 9 to 13 in which the amount of sulphur dioxide used is from 1.2-1.5 molar equivalents, relative to the disulphide of formula (III).

15. A process according to any one of claims 9 to 14 in which the amount of formate salt used relative to the disulphide of formula (III) is from 4-6 molar equivalents,

16. A process according to any one of claims 9 to 15 which further comprises using the resulting compound of formula (II) as a starting material in the process as defined in any one of claims 1 to 8.

17. A process (C) for the preparation of a disulphide of formula (III) as defined in claim 9; which process comprises adding sulphur monochloride (S_2Cl_2) to a solution, in an organic solvent, of a compound of formula (IV):



(IV)

wherein R^1, R^2 and W are as defined in claim 1.

18. A process according to claim 17 in which the solvent is selected from toluene, dichloromethane or dichloroethane, or aliphatic or aromatic nitriles such as acetonitrile, propionitrile, methylglutaronitrile and benzonitrile; or mixtures thereof, optionally as a mixture with chlorobenzene.

19. A process according to claim 17 or 18 in which the solvent is acetonitrile.

20. A process according to claim 17, 18 or 19 in which the sulphur monochloride is from 99.4-99.9% w/w pure.

21. A process according to any one of claims 17 to 20 in which, when acetonitrile is employed as solvent, the content of water is <1000ppm, the content of ethanol is <1500ppm and the content of ammonia is <100ppm.

22. A process according to any one of claims 17 to 21 in which the time for the sulphur monochloride addition is 1-10 minutes.

23. A process according to any one of claims 17 to 22 in which the reaction temperature of the mixture at the start of the addition of the sulphur monochloride is from 5 to 25°C.

24. A process according to any one of claims 17 to 23 which further comprises purifying the disulphide of formula (III) by:

a) heating the reaction mixture containing the disulphide under reduced pressure to remove hydrogen chloride;

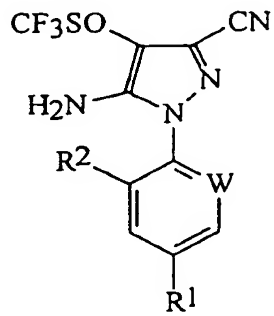
b) heating the resulting degassed reaction mixture at atmospheric pressure, followed by cooling to about 30°C;

c) adjusting the pH of the reaction mixture to 6.5-7 by addition of a weak base; and

d) cooling the mixture to a temperature of about 5 °C and isolating the desired disulphide by filtration.

25. A process according to any one of claims 17 to 24 which further comprises using the resulting disulphide of formula (III) as a starting material in a process as defined in any one of claims 9 to 16.

26. A process for the preparation of a compound of formula (I):



(I)

wherein W represents nitrogen or $-CR^3$;

R^1 represents halogen, haloalkyl, haloalkoxy, $R^4S(O)_n$-, or $-SF_5$;

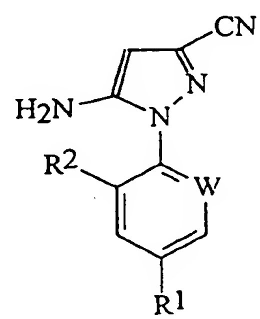
R^2 represents hydrogen or halogen;

R^3 represents halogen;

R^4 represents alkyl or haloalkyl; and

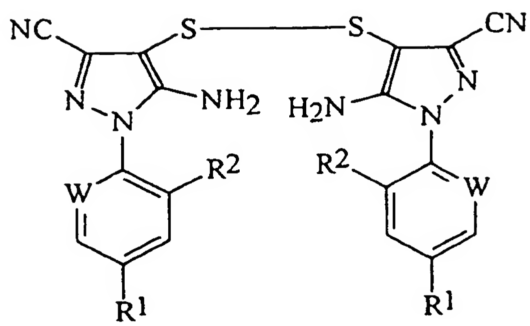
n represents 0,1 or 2; which process comprises:

(a) adding sulphur monochloride (S_2Cl_2) to a solution, in an organic solvent, of a compound of formula (IV):



(IV)

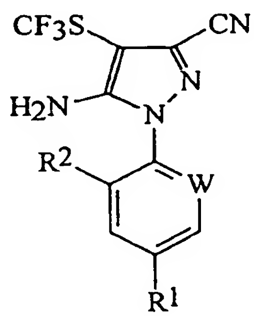
wherein R^1, R^2 and W are as defined above, to produce a disulphide of formula (III):



(III)

wherein R^1, R^2 and W are as defined above;

(b) adding sulphur dioxide to a mixture comprising the said disulphide of formula (III), a formate salt, trifluoromethyl bromide and a polar solvent, to produce a compound of formula (II):



(II)

wherein R^1, R^2 and W are as defined above; and

(c) oxidising the said compound of formula (II) with trifluoroperacetic acid in the presence of a corrosion inhibiting compound.

27. A process according to any one of claims 1 to 8 or 26 in which the compound of formula (I) is:

5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole.

28. A process according to any one of claims 9 to 16 or 26 in which the compound of formula (II) is:

5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthiopyrazole.

29. A process according to any one of claims 17 to 26 in which the compound of formula (III) is:

5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyanopyrazol-4-yl disulphide.

30. A process according to any one of the preceding claims in which:

R^1 represents trifluoromethyl, trifluoromethoxy or $-SF_5$;

W represents $-CR^3$; and

R^2 and R^3 represent chlorine.

31. A compound of formula (I) as defined in claim 1 when produced by a process as defined in any one of claims 1, 16 or 26.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/08687

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/44 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 374 061 A (RHONE POULENC AGROCHIMIE) 20 June 1990 (1990-06-20) cited in the application claims	1-31
A	EP 0 668 269 A (RHONE POULENC AGROCHIMIE) 23 August 1995 (1995-08-23) claims	1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

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